A-20482.CON PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Patent Application of)
)
Alan Patterson et al.)
)
Serial No.) Prior Application:
) Examiner: J. Goldberg
Filed: Herewith) Art Unit: 1614
)
For: LONG-ACTING OXYTETRACYCLINE)
COMPOSITION)

CONTINUATION APPLICATION UNDER 37 C.F.R. 1.53(b)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is a request for filing a continuation application under 37 C.F.R. 53(b), of pending prior application Serial No. 08/765,475 of Alan Patterson et al., filed on January 9, 1997, for LONG-ACTING OXYTETRACYCLINE COMPOSITION.

1. Submitted herewith is a complete copy of application Serial No. 08/765,475 including the declaration as originally filed and claims as annexed to the International Preliminary Examination Report in PCT/GB95/01583, of which Serial No. 08/765,475 is the U.S. nationalization. The copy of the papers of the prior application as filed and which are submitted herewith are as follows:

7 pages of specification
2 pages of claims
2 pages of declaration

2. The filing fee is calculated below:

CLAIMS AS FILED IN THE PRIOR APPLICATION
LESS ANY CLAIMS CANCELED BY AMENDMENT HEREWITH

Basic Fee	$395.00
Total Claims 20 - 20 = 0 X $22	- 0 -
Independent Claims 2 - 3 = 0 X $74	- 0 -
Total	$395.00

3. A verified statement claiming small entity status was filed in application Serial No. 08/765,475, and small entity status is still proper.

4. A check in the amount of $395.00 is attached. The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 12-0275:

(x) Any additional filing fees required under 37 C.F.R. Section 1.16

(x) Any patent application processing fees under 37 C.F.R. Section 1.17. However, payment of issue fees under 37 C.F.R. Section 1.18 is NOT authorized.

5. The power of attorney in the parent application is to Richard L. Aitken, Registration No. 18,791; Clifton E. McCann, Registration No. 29,565; John P. Shannon, Registration No. 29,276; Andrew C. Aitken, Registration No. 36,729; David D'Zurilla, Registration No. 36,776; Laurence J. Marhoefer, Registration No. 21,091 and Mark A. Wurm, Registration No. 31,682.

7. A preliminary amendment is attached.

8. Please direct all correspondence regarding this application to the undersigned.

Respectfully submitted,

John P. Shannon
Reg. No. 29,276

Date: 9-24-98

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A-20482.CON PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Patent Application of	)	
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Alan Patterson et al.	)	
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Serial No.	)	Prior Application:
(continuation of 08/765,475)	)	Art Unit: 1614
	)	Examiner: J. Goldberg
Filed: concurrently herewith	)	
	)	
For: LONG-ACTING OXYTETRACYCLINE COMPOSITION	)	

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination on the merits, please amend the above-identified application as follows:

In the Specification:

Page 1, between lines 1 and 2, insert:

--This application is a continuation of application Serial No. 08/475,768 of Alan Patterson et al., filed January 9, 1997, entitled "LONG-ACTING OXYTETRACYCLINE COMPOSITION"--.

Page 2, line 1, change "oxtetracycline" to --oxytetracycline--.

In the Claims:

Amend claim 1 as follows:

1. (Amended) A composition containing as active principle an amount of a tetracycline compound effective for antibiotic activity, either as the free base or a salt thereof with a

physiologically acceptable acid, complexed with a substantially equimolar amount of a magnesium compound, solubilised in a water miscible solvent system comprising,

a) glycerol formal in an amount of from about 10 to about 50% v/v; with

b) polyethylene glycol in an amount of from about 1 to 15% v/v;

said composition optionally containing a pH modifier in an amount sufficient to maintain a physiochemically acceptable pH, the balance being made up with water q.s.

Claim 3, line 1, delete "or claim 2"; and

Claim 4, line 1, delete "or claim 2".

Cancel claim 10.

Add the following claims:

11. (New) A composition according to claim 2 wherein the magnesium compound is magnesium oxide.

12. (New) A composition according to claim 2 wherein the magnesium compound is a magnesium salt.

13. (New) A composition containing as active principle a tetracycline compound in an amount of from about 15 to about 35% w/v, either as the free base or a salt thereof with a physiologically acceptable acid, complexed with a substantially equimolar amount of a magnesium compound, solubilised in a water miscible solvent system comprising,

a) glycerol formal in an amount of from about 10 to about

50% v/v; with

b) polyethylene glycol in an amount of from about 1 to 15% v/v;

said composition optionally containing a pH modifier in an amount sufficient to maintain a physiochemically acceptable pH, the balance being made up with water q.s.

14. (New) A composition according to claim 13 comprising as a thickener polyvinyl pyrrolidone in an amount of up to about 10% w/v.

15. (New) A composition according to claim 13 wherein the magnesium compound is magnesium oxide.

16. (New) A composition according to claim 13 wherein the magnesium compound is a magnesium salt.

17. (New) A composition according to claim 16 wherein the magnesium salt is magnesium chloride.

18. (New) A composition according to claim 13 wherein the tetracycline compound is oxytetracycline base or its hydrochloride.

19. (New) A composition according to claim 13 wherein the composition contains about 30% w/v oxytetracycline, about 40% glycerol formal, about 10% v/v polyethylene glycol with a magnesium-containing complexing agent or stabilizer, antioxidant and water making up the balance.

20. (New) A composition according to claim 19 wherein magnesium oxide is present in an amount of about 2.7% w/v and, as antioxidant, sodium formaldehyde sulphoxylate in an amount of about 0.4% w/v may be used.

21. (New) A composition according to claim 1 wherein the polyethylene glycol is polyethylene glycol 200.

REMARKS

Claim 21 was presented in an Amendment under 37 C.F.R. 1.116 in the parent application.

Respectfully submitted,

Date: 9-24-98

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Long-Acting Oxytetracycline Composition

This invention relates to injectable formulations containing tetracyclines, particularly oxytetracycline, which exhibit higher residual effect with less of the known detrimental effects such as pain at injection site, swelling, tissue irritancy or necrosis.

Preparation of pharmaceutical compositions containing tetracyclines and oxytetracycline in particular has always presented a challenge due to aqueous solubility constraints which firstly have impact upon composition stability, and secondly upon parenteral administration.

Prior art oxytetracycline compositions have exhibited relatively high viscosity at low temperatures which makes injection difficult, have shown poor stability and suffered limitations on strength of active principle. Thus considerable research has gone into determining suitable complexing agents and more favourable co-solvents to address these shortcomings. A review of the art suggests that presence of calcium, and especially magnesium in the formulation now appears mandatory as a complexing agent and whereas some improvements have been made in stability and delivery by adopting various co-solvent systems, higher concentration loadings and residual effect remain areas in which improvements are needed. This is especially of interest for veterinary purposes where the need is to deliver high effective doses with minimum effort in animal handling and detrimental effect on the animal requiring treatment.

At the current time prior art so-called "long-acting" oxytetracycline formulations typically contain 200 mg/ml oxytetracycline and are administered at 20 mg/kg body weight, having activity as determined by residual blood levels of oxytetracycline detectable for up to about four days or so.

An object of this invention is to provide a composition of substantially greater long acting effect whilst minimising to the greatest extent possible the defects observed in previously proposed formulations. In particular the invention to be particularly described hereinbelow

provides for administration of an oxtetracycline formulation at dose rates of from 10 to 40 mg/kilogram bodyweight, giving at 30 mg/kg in animals an extended duration of effective plasma levels against susceptible organisms in excess of 9 days which is a surprising achievement in the light of the known prior art.

Solubility of oxytetracycline in non-aqueous solvents was considered by Eugene Gans and Takeru Higuchi, Journal of the American Pharmaceutical Association, 1957, *Vol XLVI*, pp 587-591.

The patent literature in this area is extensive and one could refer to the following patents which are illustrative of the decades of research carried out on formulation of tetracycline compositions:

GB-A-894 619, GB-A-1 131 007, GB-A-1 250 304, GB-A-1 286 351, GB-A-1 427 882, GB-A-1 494 558, GB-A-1 508 601, GB-A-1 514 838, GB-A-1 520 197, GB-A-1 538 903 GB-A-1 563 478, GB-A-1 592 053, GB-B-2 047 097; EP-B-38 103, EP-B-96 942; US-A-2 516 080, US-A-2 980 584, US-A-2 990 331, US-A-3 062 717, US-A-3 219 529, US-A-3 557 280, US-A-3 712 949, US-A-3 957 972, US-A-4 011 313, US-A-4 018 889, US-A-4 020 162, US-A-4 126 680, US-A-4 386 083, US-A-4 399 127, US-A-4 772 460, US-A-4 957 972, and US-A-5 075 295.

From these documents it is apparent that a variety of water-dispersible complex-stabilisers or water-miscible co-solvents have been proposed including 2-pyrrolidone, polyvinyl pyrrolidone, polyethylene glycols, caprolactam, 2-piperidone, and glycerol formal (a reaction product of glycerol and formaldehyde) in specific formulations. However it is by no means clear that the said co-solvents are equally interchangeable nor can the effect of such a change be entirely predictable for a given formulation.

US-A-4 386 083 proposes use of glycerol formal in conjunction with magnesium acetate and magnesium chloride, whilst US-A-4 772 460 proposes use of N-methylpyrrolidone (1-methyl-2-pyrrolidone) and a soluble magnesium compound.

US-A-5 075 295 is particularly directed to a composition aiming to achieve up to 30% oxytetracycline, which contains polyethylene glycol 400 and magnesium oxide, but examples given only appear to show a capability of achieving up to 25% oxytetracycline and there is to applicant's knowledge no current commercially available product capable of achieving greater than 20%.

Accordingly this invention provides a composition containing as active principle a tetracycline compound, either as the free base or a salt thereof with a physiologically acceptable acid, complexed with a substantially equimolar amount of a magnesium compound, solubilised in a water miscible solvent system comprising, either

(i) a) glycerol formal in an amount of from about 10 to about 50% v/v; with

b) polyethylene glycol in an amount of from about 1 to 15% v/v; or

(ii) from about 25 to about 75% v/v of N-methylpyrrolidone,

said composition optionally containing a pH modifier in an amount sufficient to maintain a physiochemically acceptable pH, the balance being made up with water q.s.

The composition optionally contains a thickener such as polyvinyl pyrrolidone in an amount of up to 10% w/v, and may contain usual formulation aids or auxiliaries typically used for such formulations. Thus the composition may contain antioxidants, e.g. sodium formaldehyde sulphoxylate and pH adjusting agents e.g. monoethanolamine, to provide a preferred pH range of from about 7.5 to about 9.5, more preferably from about 8.5 to about 9.0.

Preferably the composition contains a magnesium compound such as magnesium oxide or a salt e.g magnesium chloride.

The preferred compositions contain oxytetracycline as the base or its hydrochloride in an amount of from about 15 to about 35% w/v, complexed with an equimolar ratio of a magnesium compound, preferably a salt, solubilised in a solvent system comprising polyethylene glycol in an amount

of from about 1 to about 15% v/v and glycerol formal in an amount of from about 10 to about 50% v/v. In particular the most preferred composition contains about 30% w/v oxytetracycline, about 40% glycerol formal, about 10% v/v polyethylene glycol with a magnesium-containing complexing agent or stabiliser, antioxidant and water making up the balance. In that composition magnesium oxide is suitably present in an amount of about 2.7% w/v and, as antioxidant, sodium formaldehyde sulphoxylate in an amount of about 0.4% w/v may be used. Thus according to the present invention there is provided a formulation capable of providing from about 10 to about 40 mg/kg bodyweight consisting of:

Oxytetracycline	300 mg
Magnesium oxide	27 mg
Sodium formaldehyde sulphoxylate	4 mg
Glycerol formal	0.4 ml
Polyethylene glycol	0.1 ml
Monoethanolamine	q.s. pH 8.6 to 8.8
Water for injections	to 1 ml

The invention will now be further described by way of example for the purposes of practical illustration only.

An oxytetracycline formulation was prepared according to the procedure indicated below using the following components:

Active Ingredient -

Oxytetracycline	30% w/v

Excipients -

Magnesium oxide	2.7% w/v
Sodium formaldehyde sulphoxylate	0.4% w/v
Glycerol formal	40% w/v
Polyethylene glycol	10% w/v
Monoethanolamine	q.s. pH 8.6 to 8.8
Water for injections	to 100% w/v

A controlled environment having an inert atmosphere was provided within which suitable mixing and temperature controllable heating apparatus was assembled. A nitrogen blanket is considered suitable for this purpose. The above

components of the proposed composition were mixed by initially mixing a proportion of the total water with the selected solvents. The sodium formaldehyde sulphoxylate, magnesium oxide and oxytetra-cycline were added sequentially whilst mixing continuously and maintaining a temperature of approximately 65°C until all the constituents have dissolved. Thereafter, the composition is cooled to below 30°C and the pH is adjusted to lie within the range of 8.0 to 9.0, in this case by adding a sufficient amount of mono-ethanolamine. Finally the volume is made up with water, the pH checked and adjusted if necessary, and the composition is filtered through a 0.2 μm filter and filled into appropriate containers.

In alternative embodiments, where use of a thickener such as polyvinyl pyrrolidone is called for then it should preferably be added after the sodium formaldehyde sulphoxylate.

The following Tables provide details of Examples 1 to 14 each of which provided compositions showing excellent stability and which achieved the desired dosage levels and long acting effect.

TABLE 1:

INGREDIENTS	EXAMPLE									
	1	2	3	4	5	6	7	8	9	10
Oxytetracycline (% w/v)	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	15.0	35.0
Magnesium Oxide (% w/v)	2.7	2.7	2.7	2.7	2.7	2.7	2.7	13.25*	1.3	3.06
Sodium Formaldehyde Sulphoxylate (% w/v)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.4	0.4
Glycerol Formal (% v/v)	30.0	30.0	30.0	35.0	35.0	35.0	40.0	40.0	40.0	40.0
Polyethylene Glycol 200 (% v/v)	10.0	15.0	20.0	10.0	15.0	20.0	10.0	10	10.0	10.0
Polyvinyl Pyrrolidone K12 (% w/v)			3.0							
Water to (% v/v)	100	100	100	100	100	100	100	100	100	100

*Magnesium Chloride

TABLE 2:

INGREDIENTS	EXAMPLE			
	11	12	13	14
Oxytetracycline (% w/v)	30	30	25	35
Magnesium Oxide (% w/v)	2.78	2.78	2.3	3.21
N-Methyl Pyrrolidone (% v/v)	30.0	60.0	60.0	60.0
Sodium Formaldehyde Sulphoxylate (% w/v)	0.4	0.4	0.40	0.4
Water to (% v/v)	100	100	100	100

AMENDED CLAIMS

[received by the International Bureau on 16 January 1996 (16.01.96);
original claims 1 and 10 amended; remaining claims unchanged (2 pages)]

1. A composition containing as active principle a tetracycline compound, either as the free base or a salt thereof with a physiologically acceptable acid, complexed with a substantially equimolar amount of a magnesium compound, solubilised in a water miscible solvent system comprising,

a) glycerol formal in an amount of from about 10 to about 50% v/v; with

b) polyethylene glycol in an amount of from about 1 to 15% v/v;

said composition optionally containing a pH modifier in an amount sufficient to maintain a physiochemically acceptable pH, the balance being made up with water q.s.

2. A composition according to claim 1 comprising as a thickener polyvinyl pyrrolidone in an amount of up to about 10% w/v.

3. A composition according to claim 1 or claim 2 wherein the magnesium compound is magnesium oxide.

4. A composition according to claim 1 or claim 2 wherein the magnesium compound is a magnesium salt.

5. A composition according to claim 4 wherein the magnesium salt is magnesium chloride.

6. A composition according to claim 1 wherein the tetracycline compound is oxytetracycline base or its hydrochloride in an amount of from about 15 to about 35% w/v.

7. A composition according to claim 1 wherein the composition contains about 30% w/v oxytetracycline, about 40% glycerol formal, about 10% v/v poly-ethylene glycol with a magnesium-containing complexing agent or stabiliser, antioxidant and water making up the balance.

8. A composition according to claim 7 wherein magnesium oxide is present in an amount of about 2.7% w/v and, as antioxidant, sodium formaldehyde sulphoxylate in an amount of about 0.4% w/v may be used.

9. An injectable composition for treatment of animals which consists of:

Oxytetracycline	300 mg
Magnesium oxide	27 mg
Sodium formaldehyde sulphoxylate	4 mg
Glycerol formal	0.4 ml
Polyethylene glycol	0.1 ml
Monoethanolamine	q.s. pH 8.6 to 8.8
Water for injections	to 1 ml, the

said composition providing for administration of from about 10 to about 40 mg of oxytetracycline per kilogram of bodyweight.

10. An injectable composition for treatment of animals according to any one of the Examples 1 to 10 hereinbefore.

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled "LONG-ACTING OXYTETRACYCLINE COMPOSITION", the specification of which

(check one) ___ is attached hereto.

___ was filed as United States Application

Serial No. _____

on _____

and was amended

on _____ (if applicable).

_x_ was filed as PCT international application

Number PCT/GB95/01583

on 5 July 1995

and was amended under PCT Article 19

on 21 July 1995 (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information which I know to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international applications(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) on which priority is claimed:

Prior Foreign Application(s)

(Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed
9413873.2	Great Britain	9 July 1994	X Yes ___No
			X Yes ___No
			___Yes ___No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international applications(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations,

§1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application.

(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)
(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)
(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Joseph M. Lane, Registration No. 18,278; Richard L. Aitken, Registration No. 18,791; Clifton E. McCann, Registration No. 29,565; John P. Shannon, Registration No. 29,276; Andrew C. Aitken, Registration No. 36,729; David D'Zurilla, Registration No. 36,776; and Laurence J. Marhoefer, Registration No. 29,091.

Address all telephone calls to John P. Shannon at telephone number (202)337-5556

Address all correspondence to: Lane, Aitken & McCann
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2600 Virginia Avenue, N.W.
Washington, D.C. 20037

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

X Full name of sole or first inventor (given name, family name) Alan Patterson

X Inventor's signature _____ Date: X 11 FEBRUARY 1997

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Inventor's signature _____ Date: _____

Residence _____ Citizenship: _____

Post Office Address _____

Full name of fourth joint inventor, if any (given name, family name) _____

Inventor's signature _____ Date: _____

Residence _____ Citizenship: _____

Post Office Address _____

PRINT OF DRAWINGS
AS ORIGINALLY FILED

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Office of Initial Patent Examination -- Scanning Division

Application deficiencies found during scanning:

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